REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claims 1 and 9 have been amended. More particularly, claim 1 has been amended to recite that a molar ratio of said basic compound is 1 to 30 mol% of total liposome membrane constituents and a molar ratio of said acidic compound is 0.5 to 30 mol% of total liposome membrane constituents. Support for such amendment can be found throughout the originally filed application, including original claims 2 and 3. Claim 9 has been amended to be dependent upon claim 8. Further, by the foregoing amendment, claims 2-3 and 19 have been canceled without prejudice or disclaimer to the subject matter recited therein. No new matter has been added.

Turning now to the Official Action, claims 17-19 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. This rejection is respectfully traversed.

As to claim 17, the Examiner has requested clarification as to whether chondroitin sulfate (as recited in line 8) is the drug (as recited in line 3). In response, applicants submit that chondroitin sulfate is not a drug. Chondroitin sulfate is a kind of glycosaminoglycan distributed on the cell membrane or extracellular matrix. Chondroitin sulfate is produced in many cells and is expressed in a certain type of cancer cells as the

cancer malignancy is increased. In the present invention, the liposome has target directivity and chondroitin sulfate is used for an assumed target. Therefore, chondroitin sulfate is not used as a membrane constituent of the liposome or a drug contained in the liposome.

Claims 18 and 19 have been rejected for recitation of the phrase "drug for a therapy and/or diagnosis" because, according to the Examiner, there is no diagnostic agent in the claim. Initially, it is noted that claim 19 has been canceled. Thus, the Examiner's rejection of claim 19 has been rendered moot. As to claim 18, applicants respectfully disagree with the Examiner's allegation that there is no diagnostic agent present in the claims. Contrary to the Examiner's assertion, claim 18 specifically recites "a drug intended for the therapy and/or diagnosis . . . ." (Emphasis added.)

Claim 19 has further been rejected for reciting a use without any active steps. However, as indicated above, claim 19 has been canceled thereby rendering the Examiner's rejection moot.

In view of the above, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 112, second paragraph.

The Examiner has rejected claims 19 under 35 U.S.C. § 101. Once again, since claim 19 has been canceled, the Examiner's rejection has been rendered moot.

Accordingly, withdrawal of this rejection under 35 U.S.C. § 101 is respectfully requested.

Claims 1-5, 7, 10-11, 13-16 and 18-19 have been rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by EP 0 636 363 ("EP '363"). This rejection is respectfully traversed.

The Federal Circuit has held that for prior art to be anticipatory, every element of the claimed invention must be disclosed in a single item of prior art in the form literally defined in the claims. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). This requirement for anticipation has not been met with respect to the currently pending claims.

Independent claim 1, for example, recites:

> A liposome that includes a drug intended for the therapy and/or diagnosis, comprising as membrane constituents [1] a basic compound, [2] an acidic compound which is a phosphoric acid monoester derivative, or a compound having a carboxyl group or its salt, and [3] a liposome membrane constituent other than [1] and [2], that is accumulated at a diseased site at pH 5 to 7, wherein a molar ratio of said basic compound is 1 to 30 mol% of total liposome membrane constituents and a molar ratio of said acidic compound is 0.5 to 30 mol% of total liposome membrane constituents.

The object of the present invention is to provide a liposome that exhibits target directive capability by a change in pH at a diseased site. The liposome of the present invention is very weakly cationic in a physiological pH condition and strongly cationic enough to interact with a substance having a negative charge in an acidic condition by containing a basic compound and an acidic compound in specified amounts. The liposome of the present invention is very weakly cationic in the physiological pH condition because of the ionization of both the basic compound and the acidic compound at fixed rates and hence does not interact with a substance having a negative charge such as cell or protein.

However, the ionization of the acidic compound is suppressed in the acidic condition, so that the liposome is made cationic enough to interact with a substance having a negative charge at a target site where pH is decreased such as an inflammatory site or a tumor site, whereby its affinity for cells is improved, and the liposome is efficiently accumulated at the target site but its accumulation outside the target site is prevented.

The object of the present invention is achieved by the construction and mechanism as described above and the effects obtained are demonstrated in Examples of the present invention.

EP '363 describes a liposome and use of a compound containing an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group in the liposome. Phosphatidic acid is mentioned as an example of phospholipid, and glucuronic acid and silaic acid as examples of the surface modifying agent. Thus, the "compound containing an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group" in EP '363 may correspond to the "basic compound" of the present invention, and the "glucuronic acid and silaic acid" in EP '363 may correspond to the "acidic compound" of the present invention.

However, EP '363 fails to teach, by way of example or otherwise, a compound containing an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group which is used in the amount specified in the presently claimed invention **in combination with** the specified amount of phosphatidic acid, glucuronic acid or silaic acid as recited in the claimed invention.

Since EP '363 fails to teach a basic compound and an acidic compound in the amounts specified in the claimed invention, EP '363 fails to teach every element of the claimed invention. As such, EP '363 cannot anticipate the claimed invention. Therefore, withdrawal of the rejection under 35 U.S.C. § 102(b) over EP '363 is respectfully requested.

Claims 1-5, 7, 10-16, and 18-19 have been rejected under 35 U.S.C. § 102(b) as purportedly being anticipated by JP 09 263579 (JP '579). This rejection is similarly traversed.

JP '579 describes a liposome and use of a piperidine derivative in the liposome. Phosphatidic acid is mentioned as an example of phospholipid and glucuronic acid and silaic acid as examples of the surface modifying agent. Therefore, the "piperidine derivative" may correspond to the "basic compound" of the present invention and the "glucuronic acid and silaic acid" may correspond to the "acidic compound" of the present invention.

However, just as with EP '363, JP '579 fails to teach, by way of example or otherwise, a compound containing an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group which is used in the amount specified in the presently claimed invention in combination with the specified amount of phosphatidic acid, glucuronic acid or silaic acid as recited in the claimed invention.

JP '579 cannot anticipate the claimed invention since it fails to teach a basic compound and an acidic compound in the amounts specified in the claimed invention.

Accordingly, withdrawal of the rejection under 35 U.S.C. § 102(b) over JP '579 is respectfully requested.

The Examiner has rejected claims 1-5, 7 and 10-19 under 35 U.S.C. § 103(a) as allegedly being unpatentable of EP '363 or JP '579. Both of these rejections are respectfully traversed.

As discussed above, EP '363 and JP '579 fail to teach a basic compound and an acidic compound in the amounts specified in the claims. Moreover, there is no suggestion in either EP '363 or JP '579 to combine such compounds in the specified amounts to make the liposome surface electrically neutral in the physiological pH condition and electrically cationic in the acidic condition, and the capability of exhibiting the target directivity promptly by the pH change.

Therefore, it would not have been obvious to one skilled in the art to select phosphatidic acid, glucuronic acid or silaic acid from among various compounds described in EP '363 and JP '579 and use the selected compound in a specified amount in combination with a specified amount of the compound containing an aliphatic primary or secondary amino group or the piperidine derivative for the purpose of efficiently accumulating the liposome at a target site where pH is decreased such as an inflammatory site or a tumor site.

Since neither EP '363 nor JP '579 teach or suggest the liposome of the present invention, such references cannot render the presently claimed invention obviousness. As such, withdrawal of both rejections under 35 U.S.C. § 103(a) are respectfully traversed.

Claims 8 and 9 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over EP '363 or JP '579 in view of Gold (U.S. Patent No. 6,465,188). This rejection is respectfully traversed.

As set forth above, neither EP '363 nor JP '579 teach or suggest the liposome of the present invention. The Gold patent fails to remedy the serious deficiencies of EP '363 nor JP '579.

The Gold patent was simply relied upon by the Examiner for its purported teaching of utilizing fatty acids to enhance fusion of liposomes with cellular membranes. Since EP '363 or JP '579 in view of the Gold patent do not teach or suggest a basic compound and an acidic compound in the amounts specified in the claims, a proper *prima facie* case of obviousness has not been established.

In view of the above, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully traversed.

Finally, claims 6 and 12 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over EP '363 in combination with either Schneider (U.S. Patent No. 6,258,378) and Malone (PNAS, 86:6077-81 (1989)). This rejection is also respectfully traversed.

To establish a *prima facie* case of obviousness of the claimed invention, all of the claim limitations must be taught or suggested by the combination of prior art references. *See In re Royka*, 490 F.2d 981 (C.C.P.A. 1974). Here, all of the claim limitations are not taught by the combination of references.

As discussed above, EP '363 fails to teach or suggest a basic compound in the amount specified in the presently claimed invention **in combination with** the specified amount of an acidic compound. The Schneider patent and the Malone reference do not teach or suggest all of the elements missing from EP '363. Therefore, the combination of EP '363 with the Schneider patent and/or the Malone reference fail to establish a proper *prima facie* case of obviousness.

Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is respectfully requested.

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this Amendment and Reply, or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: December 3, 2003

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